SciMedCentral

JSM Atherosclerosis

Review Article

The Role of C - reactive protein in the Cardiovascular Risk and its Association with Hypertension

Arthur F Cortez and Elizabeth S Muxfeldt*

Hypertension Program, University Hospital Clementino Fraga Filho, Schoolof Medicine, Universidade Federal do Rio de Janeiro

***Corresponding author**

Elizabeth Silaid Muxfeldt, Hypertension Program, University Hospital Clementino Fraga Filho, Schoolof Medicine, Universidade Federal do Rio de Janeiro, Rua Homem de Melo, 150/102-CEP 20510-180 Tijuca, Rio de Janeiro RJ, Brazil, Tel: 55-21-3938-2514; Email: bethmux@globo.com

Submitted: 11 October 2016

Accepted: 02 November 2016

Published: 03 November 2016

Keywords

- Cardiovascular risk
- C-reactive protein
- Hypertension
- Prognosis

Abstract

Chronic and long-lasting inflammation is the beginning of the endothelial dysfunction process and atherosclerosis. Thus, C-reactive protein (CRP) initially described as an acute phase protein is a marker of cardiovascular disease but not so early on and specific. The association between CRP and the development of hypertension and cardiovascular disease has been revealed, but not completely understood, since the cause-effect relationship and the reduction of them has not been consistently demonstrated.

Despite the established cut-off points in the healthy adult population, high sensitivity CRP (hsCRP) needs new thresholds due to the wide variability among individuals by genetic and behavioral factors. The CRP levels should be taken into account the accumulation of conditions such as obesity, diabetes mellitus, old age and hypertension. Nevertheless, clinical evidence supports a modest benefit in cardiovascular risk prediction in the intermediate risk group by the Framingham risk score.

This article approaches the applicability of hsCRP in clinical practice looking for the capacity to stratify and to refine cardiovascular risk assessment. We searched if there is any hsCRP utility on driving CV risk treatment. Some favorable evidence about the association between CRP and the development of hypertension were checked over. However, CRP could not be separate of dietary and metabolic factors, namely obesity. Finally, analysis of the prospective studies of CRP as a prognostic factor in hypertension were done including high-normal blood pressure person, hypertensive's and resistant hypertensive's.

ABBREVIATIONS

CRP: C - Reactive Protein; Hscrp: High Sensitivity CRP; CV: Cardiovascular; CHD: Coronary Heart Disease; FRS: Framingham Risk Score; RRS: Reynolds Risk Score; Preht: Pre-Hypertension

INTRODUCTION

Since its discovery in 1930 by a reaction with the C capsular polysaccharide of Streptococcus pneumonia [1] C-reactive protein (CRP) has been studied in inflammatory processes. Originally, it is known as acute phase protein produced in the liver participating in the recognition and activation of inflammation, especially in the innate immune system [2].

For twenty years, the measurement of high-sensitivity CRP was related to cardiovascular (CV) risk without infection or tissue damage [3]. This knowledge has improved since atherosclerosis, the main agent of CV disease, came to be understood as a chronic and long-lasting inflammation of the blood vessels leading to coronary heart disease (CHD), peripheral artery disease and stroke. Therefore, pharmacologically CRP reduction can possibly minimize the development of CV events [4].

This paper reviews three end-points from the literature to better understand the current state and applicability of high-sensitivity C-reactive protein (hsCRP) in clinical practice: (1) Cardiovascular risk prediction; (2) Association between CRP and hypertension; (3) CRP as a prognostic factor in hypertension

Cardiovascular risk prediction

In 2003, the American Heart Association published a statement by setting hsCRP cutoff points from cohort studies in apparently healthy populations, guiding the dosage of the protein in those at intermediate CV risk by the Framingham score (multiple risk factor scoring projects 10-year CHD risk in the range of 10% to 20%) [5]. The established cut points of low risk (<1.0 mg/l), average risk (1.0 to 3.0 mg/l), and high risk (

>3.0 mg/l) correspond to approximate tertiles of hsCRP in the adult population. These thresholds are based on distributions of hsCRP samples in over 40 thousand persons gathered, however it is extremely unlikely that CRP modify the stratification such as low-risk people (<10% per 10 years) to have a high risk (>20% risk over 10 years).

Within reason, who are at high risk or with established atherosclerotic disease generally should be treated intensively regardless of their hsCRP levels [6]. To date, the hsCRP utility as a public health remains in doubt and guidelines recommends against screening of the entire adult population [7-9]. Some of the reasons for this issue are: 1- the main studies were carried out in European and American (Asians tend to have lower CRP values) [10]; 2- consistent differences between men and women favoring mostly evidences about higher values in men; 3-wide variability among individuals and in the same person [11]; 4-need for age stratification [11]; 5-influence of other factors such as aspirin and statin use, smoking, visceral obesity [12], diabetes and metabolic syndrome [13].

Thereafter, some researchers plead that association between hsCRP and CV diseases is due to a strong correlation with traditional risk factors. Thus, this biomarker did not allow us to discriminate CV events in all people independently of conventional risk assessment because of relative collinearity within Framingham risk score (FRS) variables. The Reynolds risk score (RRS) adds hsCRP level and CHD family history to conventional parameters considered in the FRS. Although both scores are predictive of CV risk, the RRS has been shown as additional predictive power in atherosclerosis progression. In spite of a small amount contribution of CHD family history and even less of hsCRP, the RRS seemed to be better and useful when discordance exists between the two scoring systems [14].

The CRP advantages are: firstly, the substance is easily dosed showing quantitative differences in patients with and without coronary artery disease; secondly, CRP levels behave to be stable over time in the same individual to the same extent as other biochemical and physical attributes [15]. Clinical evidence supports a modest benefit in cardiovascular risk prediction in a specific group (intermediate risk by the FRS). Notwithstanding the proven association between elevations of CRP levels and CV diseases, measurement of protein should not be used to exclude disease (low negative predictive value), either, for driving treatment [9].

Concerning the benefit effect on cardiovascular events and hsCRP under statin treatment, Server et al., researched baseline and on-treatment hsCRP levels with cardiovascular events among hypertensive patients in the ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial Lipid-Lowering Arm) [6]. Again, baseline hsCRP levels predicted incident CV diseases, even though no difference was detected in the relative effect of statin therapy on tertiles of CRP. Although achieving LDL-C levels below the median at 6 months was associated with lower CV diseases risk, a clear risk reduction was not seen for hsCRP levels below the median in fully adjusted models.

Previously, Ridker et al., suggested that baseline hsCRP levels distinguished which patients with relatively low LDL-C levels have benefited from statin therapy [16]. In the JUPITER study, post hoc analysis better powered for on-treatment analysis, proposed that lower hsCRP levels may indicate greater degrees of success with statin treatment [17]. Moreover, in the Heart Protection Study with over twenty thousand at-risk individuals bridging the primary and secondary prevention spheres, statin therapy conferred a 29% relative risk reduction even if baseline hsCRP was <1.25 mg/l [18].

A previous meta-regression analysis found that the degree of risk reduction conferred by statins is completely compatible with the degree of LDL-C lowering rather than additional pleiotropic effects [19]. In brief, there is inconsistent evidence regarding the utility of hsCRP measurements for targeting statin therapy for primary prevention.

Association between CRP and hypertension

Despite the great number of factors and conditions associated with CV disease and elevated CRP levels, high blood pressure (BP) are well established as a cardiovascular risk factor. CRP could be not only a marker of atherothrombosis process, but also a mediator of this mechanism. Although CRP has emerged as a predictor of future cardiovascular events, the mechanism in which the protein and hypertension promotes atherogenesis remains obscure [20]. The question remains open: What is the role of hypertension in vascular inflammation?

In order to explain this mechanism, a large cohort study followed around 15,000 apparently healthy women for eight years [21]. In summary, after adjustment of known variables as risk factors (age, BMI, diabetes, smoking, LDL and HDL cholesterol), the authors showed that increased categories of BP levels was related to higher CRP values. In prospective analyses, both elevated CRP levels (≥ 3 mg/l) and increasing BP categories were independent determinants of future cardiovascular events, and CRP had incremental prognostic value at all BP levels. One possibility would be a direct effect of the pressure in the vessels through known routes of adhesion of inflammatory cells promoting vasoconstriction. Meanwhile, the reverse thinking can be postulated: the vascular inflammation and CRP could provide hypertension. It should to be noted that in the aforementioned study, CRP increased along with the BP levels hindering cause-effect relationship.

Sesso et al., followed more than 5,000 women who developed hypertension from more than 20,000 people enrolled for almost 8 years. Those in the highest CRP quartile had twofold risk of developing hypertension than women in the lowest quartile. The inclusion of CRP only marginally improved the prediction of incident hypertension [22]. Back then, two other studies found associations between CRP and the risk of hypertension development [23,24].

Recently, nested case-control studies showed association between baseline CRP levels [25] or increasing CRP levels [26] and risk of hypertension, losing significance after adjustment for body mass index (BMI). However, CRP has been associated with the risk of hypertension even after adjustment for abdominal obesity in two other cohorts of middle-aged men and women [27,28].

All these studies [21-28] that showed whether or not any risk prediction between CRP and hypertension have been concerned with traditional confounders. There is also a concern with serial measurements of inflammatory markers, and rightly to the type of population studied. It is impossible to assess and to compare so heterogeneous populations regarding the risk of developing hypertension, even if they have similar prevalence of risk factors.

Comprehensive adjustments for major risk factors for hypertension were done, while residual confounding by unavailable dietary and metabolic factors may persist. Additionally, it is important to discuss about changing lifestyle and routine use of medications, changing the CRP values but not necessarily reducing the inflammatory state. One of these questions is whether high fitness attenuates the likelihood of developing hypertension in subjects with elevated inflammatory markers [29]. Of 2,475 normotensive men, 266 (10.7%) developed hypertension during an average of 4 years' follow-up. The association of CRP and incident hypertension was shown in those in the upper tertile versus lower tertile, losing significant after adjusting for BMI. Cardio respiratory fitness was analyzed for same multivariate adjustment decreasing 27% of the risk of incident hypertension compared fit to unfit participants. In the joint analysis, unfit men with upper CRP had 1.81 times greater risk of hypertension development compared to fit men with low CRP, even though this risk did not significantly increase in comparison fit men with upper CRP. It was argued that endothelial dysfunction, oxidative stress and arterial stiffness were previously mitigated with cardio respiratory fitness. Somehow, high-fitness subjects provide vascular protection by enhanced autonomic function and by reduced cardio metabolic risk factors, including body fat and insulin resistance, independently of elevated inflammatory markers [29].

Based on these latest articles [25,29] we can hypothesize that something happens in endothelial level by promoting inflammation, and hence, rising CRP in younger individuals until middle age. These people would be in jeopardy for developing hypertension if endothelial inflammation persists due to the emergence of a pro-atherogenic metabolic status, particularly obesity. We do not know which the triggers are and we did not clarify the obscure interrelationship among CRP, endothelial dysfunction and hypertension. Whether by genetic mechanisms, acquired conditions or both, some individuals are more susceptible to progression and complications of atherosclerosis, called higher CRP responders [30].

C-reactive protein as a prognostic factor in hypertension

On one hand, the risk analysis between CRP and hypertension is complex; on the other, the prediction of adverse outcomes arising from this association is necessary. However, few prospective studies concluded about the prognosis of patients with hypertension, considering the CRP as a marker of the fates. (Table 1) As described before, Blake et al. [21], evaluated 15,215 women followed prospectively for 8 years, divided in 4 categories based on CRP and BP levels. The risk factor-adjusted hazard ratios, using low CRP/low BP as reference, increased linearly as follows: high CRP/low BP, 1.86; low CRP/high BP, 2.46, and high CRP/high BP, 2.94.

Three other large studies were conducted in Asian countries evaluating CRP in hypertensive patients [31-33]. Firstly, in order to assess the risk of ischemic stroke, 2,589 individuals from rural villages in China were followed for 9.2 years on average (total follow-up of 15 years) [31]. The subjects were stratified into four groups, considering the presence or absence of hypertension and

Table 1: Prospective studies assessing CRP prognostic value in hypertension.

Study (year)	Patients enrolled (n)	Mean age (years)	Mean follow-up (months)	Number of events	Outcome	Parameter evaluated	HR (95% CI)
Blake 2003 [22]	15,215	54 ±8	97	321	Cardiac death Nonfatal MI, nonischemic stroke, coronary revascularization	CRP ≥ 3 mg/l and BP 120–129/75–84 BP 130–139/85–89 BP 140–159/90–94 BP 160/95	1.44 † 1.38* 2.40* 2.45* 5.06*
Wang 2014 [32]	2,589	> 20y	110	76	Ischemic stroke	NT/LowCRP NT/High CRP HT/Low CRP HT/High CRP	1,00 0.84 (0.28-2.52) 1.41 (0.74-2.68) 2.66 (1.29-5.47) †
Tanaka 2010 [33]	22,676 NT – 7,625 PreHT – 5,721 HT – 9,330	40-80 yr 59 ± 10 62±0 66 ±8	32	103 16 30 97	Ischemic stroke	Normotension Prehypertension Hypertension	1,00 1.72 (0.93-3.18) 2.86 (1.65-4.95)*
Iwashima 2007 [34]	629	62 ±0.6	32	52	MI, stroke, PAD, HF	LVH / CRP < 1 mg/L LVH / CRP ≥ 1 mg/L # 2	2.21 (1.29-4.57) † 2.65 (1.55–5.46)*
Cortez 2016 [36]	476 RH	70±11	108	103	Fatal and nonfatal CV events: MI, stroke, HF, PAD	CRP > 3.0 mg/L CRP > 3.8 mg/L (median)	1.49 (0.95-2.34) 1.99 (1.29-3.06) †

Abbreviations: NT: Normotension; PreH: Pre Hypertension; HT: Hypertension; RH: Resistant Hypertension; MI: Myocardial Infarction; PAD: Peripheral Artery Diseases; HF: Heart Failure; LVH: Left Ventricular Hypertrophy

*p < 0.001, †p < 0.01, ‡p < 0.05

Multivariate Cox proportional hazard model was used to determine the hazard ratios (HRs) in all studies.

elevated CRP or not (> 1.06 mg/l log CRP). The risk of ischemic stroke according to BP and CRP levels was 2.66 times higher for the group with both high conditions, compared to the group with low CRP levels and normal BP levels. In the multivariate Cox model, hypertensive patients with high CRP had the highest risk of incident ischemic stroke among the 4 subgroups. Nonetheless, normotensive with high CRP or hypertensive patients with low CRP levels were not associated with the risk of ischemic stroke, in comparison with normotensive and low CRP levels, suggesting that the unique combination of hypertension and elevated CRP levels would be an important prognostic marker of cerebrovascular event.

While the knowledge in people with high CRP has been structured on the risk of CV events, and possibly the risk of developing hypertension, comes the interest in patients classified as pre-hypertensive (PreHT) patients or high-normal BP (systolic BP between 120 to 139 mmHg and diastolic BP between 80 and 89 mmHg) in whom are indicated changes in lifestyle to prevent disease progression. Thus, the Iwate-Kenco Study Group prospectively followed individuals with high-normal BP, normotensive, and hypertensive, relating them to the CRP levels and the incidence of ischemic stroke [32]. Of the more than 22,000 subjects from 40 to 80 years without previous CV diseases but with a great variety of risk factors, only 143 had stroke (mean follow-up 2.7 years). The bivariate analysis of the population showed a statistically significant difference between the groups, and the greater the number of known risk factors for CV diseases the higher the BP by separate groups. As expected, CRP was higher in the hypertensive group compared to normotensive, and also higher in the PreHT group compared to normotensive group. In the model with multivariate survival analysis considering the BP standard (high, pre-hypertensive and normal) and CRP levels dichotomized by the median were formed 6 subgroups. Pre-hypertensive individuals with elevated CRP levels presented greater risk of stroke than the entire normotensive group and similar risk to those with hypertension and low CRP (2.63 and 2.64, respectively; $p < 0.03$), while hypertensive patients with high CRP have had ischemic stroke risk increased by 3.5 times.

Two findings indicate that hsCRP is a relatively short-term marker for cerebrovascular risk in PreHT. The first point is the risk of ischemic stroke was not significantly increased in the total PreHT group, but was increased in the PreHT subgroup with elevated hsCRP levels. Secondly, the known relationship between pre-hypertensive patients and subclinical atherosclerosis, such as increased coronary atherosclerosis, carotid and brachial intima-media thickness and microalbuminuria increasing the risk for any cardiovascular event compared to individuals with normotension [32].

Iwashima et al., studied prospectively 629 asymptomatic hypertensive patients associating CRP levels and the presence or absence of LVH [33]. The concomitant presence of left ventricular hypertrophy (LVH) and CRP above 1 mg/l was an independent predictor of cardiovascular risk, being superior as a method of risk detection compared to measurement of either biologic marker alone. Despite the smaller number of subjects, they have used CRP levels near literature.

These associations among subclinical organ damage namely, left ventricular hypertrophy and albuminuria, were extensively described in resistant hypertension [34]. Patients with uncontrolled hypertension have higher incidence of target organ damage and poorer prognosis. Recently, it was published a Brazilian study that analyzed 476 individuals with resistant hypertension towards prognostic value of CRP [35]. The protein values were substantially higher, as expected by the concomitance of several risk factors and morbidities. After a follow up reached up 10 years, elevated CRP levels (>3.8 mg/l) predicted major fatal and nonfatal cardiovascular outcomes over and beyond traditional CV risk factors, including ambulatory BP monitoring parameters. Moreover, the usually recommended cutoff value for CRP (3.0 mg/l) had no prognostic value in this population. This is the first prospective study that evaluated the prognostic importance of CRP levels in resistant hypertension highlighting different CRP thresholds in the dependence of sex, age, ethnicity, socioeconomic status, lifestyle, metabolic profile, morbidities, others inflammatory biomarkers, and genetic predisposing.

CONCLUSION

In conclusion, currently, CRP levels should not be used to guide therapy in any cardiovascular disease, including hypertension, but it is useful to stratify and to refine subgroups of patients at CV risk. It is well known that high hsCRP levels may precede or rise together with BP levels. However, we are unable to clearly determine whether this biomarker is a guilty or just taking part of inflammatory processes involved in others associated cardiometabolic factors such as obesity.

There are strong evidence regarding prognostic value of hsCRP in patients with hypertension and also in pre-hypertensives, despite this last one presents CRP levels below than previously established (3 mg/dl). Moreover, higher blood pressures are related to higher CRP levels, and both are predictors of CV events in patients with resistant hypertension.

Despite all these evidences, it is necessary to validate this marker in other populations and conditions, allowing its use in clinical practice. Furthermore, new interventional studies could identify if the hsCRP reduction with use of statins or any other drug may reduce the cardiovascular risk, beyond the well-established BP and other CV risk factors control.

ACKNOWLEDGEMENTS

This study was supported by grants from Conselho Brasileiro de Desenvolvimento Científico e Tecnológico (CNPq) and Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ).

REFERENCES

1. Tillett WS, Francis T. Serological reactions in pneumonia with a non-protein somatic fraction of pneumococcus. J Exp Med. 1930; 52: 561-571.

2. Thompson D, Pepys MB, Wood SP. The physiological structure of human C-reactive protein and its complex with phosphocholine. Structure. 1999; 7: 169-177.

3. Kuller LH, Tracy RP, Shaten J, Meilahn EN. Relation of C-reactive protein and coronary heart disease in the MRFIT nested case-control study. Am J Epidemiol. 1996; 144: 537-547.

4. Ridker PM, Danielson E, Fonseca FAH, Genest J, Gotto AM, Kastelein JJP, et al. Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein. N Engl J Med. 2008; 359: 2195-2207.

5. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO, Criqui M, et al. Markers of Inflammation and Cardiovascular Disease: Application to Clinical and Public Health Practice: A Statement for Healthcare Professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation. 2003; 107: 499-511.

6. Sever PS, Poulter NR, Chang CL, Thom SAM, Hughes AD, Welsh P, et al. Evaluation of C-reactive protein before and on-treatment as a predictor of benefit of atorvastatin: a cohort analysis from the Anglo-Scandinavian Cardiac Outcomes Trial lipid-lowering arm. J Am Coll Cardiol. 2013; 62: 717-729.

7. US. Preventive Services Task Force1. Using nontraditional risk factors in coronary heart disease risk assessment: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2009; 151: 474-482.

8. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2016; 37: 2315-2381.

9. Greenland P, Alpert JS, Beller G, Benjamin EJ, Budoff MJ, Fayad Z, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2010; 56: 50-103.

10. Charuruks N, Laohajinda B, Rujiwanitgun S, Chaiworaporn M. Reference value for C-reactive protein and its distribution pattern in thai adults. Circ J. 2005; 69: 339-344.

11. Woloshin S, Schwartz LM. Distribution of C-reactive protein values in the United States. N Engl J Med. 2005; 352: 1611-1613.

12. Brooks GC, Blaha MJ, Blumenthal RS. Relation of C-reactive protein to abdominal adiposity. Am J Cardiol. 2010; 106: 56-61.

13. Ndumele CE, Nasir K, Conceiçao RD, Carvalho JAM, Blumenthal RS, Santos RD. Hepatic steatosis, obesity, and the metabolic syndrome are independently and additively associated with increased systemic inflammation. Arterioscler Thromb Vasc Biol. 2011; 31: 1927-1932.

14. DeFilippis AP, Blaha MJ, Ndumele CE, Budoff MJ, Lloyd-Jones DM, McClelland RL, et al. The association of Framingham and Reynolds risk scores with incidence and progression of coronary artery calcification in MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol. 2011; 58: 2076-2083.

15. Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, Thompson SG, Collins R, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Emerging Risk Factors Collaboration. Lancet. 2010; 375: 132-140.

16. Ridker PM, Rifai N, Clearfield M, Downs JR, Weis SE, Miles JS, et al. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. N Engl J Med. 2001; 344: 1959-1965.

17. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM, Kastelein JJ, et al. Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. Lancet. 2009; 373: 1175-1182.

18. Heart Protection Study Collaborative Group, Jonathan Emberson, Derrick Bennett, Emma Link, Sarah Parish, John Danesh, et al. C-reactive protein concentration and the vascular benefits of statin therapy: an analysis of 20,536 patients in the Heart Protection Study. Lancet. 2011; 377: 469-476.

19. Robinson JG, Smith B, Maheshwari N, Schrott H. Pleiotropic effects of statins: benefit beyond cholesterol reduction? A meta-regression analysis. J Am Coll Cardiol. 2005; 46: 1855-1862.

20. Yousuf O, Mohanty BD, Martin SS, Joshi PH, Blaha MJ, Nasir K, et al. High-sensitivity C-reactive protein and cardiovascular disease: a resolute belief or an elusive link. J Am Coll Cardiol. 2013; 62: 397-408.

21. Blake GJ, Rifai N, Buring JE, Ridker PM. Blood pressure, C-reactive protein, and risk of future cardiovascular events. Circulation. 2003; 108: 2993-2999.

22. Sesso HD, Buring JE, Rifai N, Blake GJ, Gaziano JM, Ridker PM. C-reactive protein and the risk of developing hypertension. JAMA. 2003; 290: 2945-2951.

23. Lakoski SG, Cushman M, Palmas W, Blumenthal R, D'Agostino RB Jr, Herrington DM. The relationship between blood pressure and C-reactive protein in the Multi-Ethnic Study of Atherosclerosis (MESA). J Am Coll Cardiol. 2005; 46: 1869-1874.

24. Davey Smith G, Lawlor DA, Harbord R, Timpson N, Rumley A, Lowe GDO, et al. Association of C-reactive protein with blood pressure and hypertension: life course confounding and mendelian randomization tests of causality. Arterioscler Thromb Vasc Biol. 2005; 25: 1051-1056.

25. Sesso HD, Jiménez MC, Wang L, Ridker PM, Buring JE, Gaziano JM. Plasma Inflammatory Markers and the Risk of Developing Hypertension in Men. J Am Heart Assoc. 2015; 4: 001802.

26. Wang L, Manson JE, Gaziano JM, Liu S, Cochrane B, Cook NR, et al. Circulating inflammatory and endothelial markers and risk of hypertension in white and black postmenopausal women. Clin Chem. 2011; 57: 729-736.

27. Lakoski SG, Herrington DM, Siscovick DM, Hulley SB. C-reactive protein concentration and incident hypertension in young adults: the CARDIA study. Arch Intern Med. 2006; 166: 345-349.

28. Wang TJ, Gona P, Larson MG, Levy D, Benjamin EJ, Tofler GH, et al. Multiple biomarkers and the risk of incident hypertension. Hypertension. 2007; 49: 432-438.

29. Jae SY, Kurl S, Laukkanen JA, Lee CD, Choi YH, Fernhall B, et al. Relation of C-reactive protein, fibrinogen, and cardiorespiratory fitness to risk of systemic hypertension in men. Am J Cardiol. 2015; 115: 1714-1719.

30. Bucova M, Bernadic M, Buckingham T. C-reactive protein, cytokines and inflammation in cardiovascular diseases. Bratisl Lek Listy. 2008; 109: 333-340.

31. Wang A, Xu T, Xu T, Zhang M, Li H, Tong W, et al. Hypertension and elevated C-reactive protein: future risk of ischemic stroke in a prospective cohort study among inner Mongolians in China. Int J Cardiol. 2014; 174: 455-456.

32. Tanaka F, Makita S, Onoda T, Tanno K, Ohsawa M, Itai K, et al. Prehypertension subtype with elevated C-reactive protein: risk of ischemic stroke in a general Japanese population. Am J Hypertens. 2010; 23: 1108-1113.

33. Iwashima Y, Horio T, Kamide K, Rakugi H, Ogihara T, Kawano Y. C-reactive protein, left ventricular mass index, and risk of cardiovascular disease in essential hypertension. Hypertens Res. 2007; 30: 1177-1185.

34. de Souza F, Muxfeldt ES, Salles GF. Prognostic factors in resistant

hypertension: implications for cardiovascular risk stratification and therapeutic management. Expert Rev Cardiovasc Ther. 2012; 10: 735-745.

35. Cortez AF, Muxfeldt ES, Cardoso CR, Salles GF. Prognostic Value of C-Reactive Protein in Resistant Hypertension. Am J Hypertens. 2016; 29: 992-1000.

Cite this article

Cortez AF, Muxfeldt ES (2016) The Role of C - reactive protein in the Cardiovascular Risk and its Association with Hypertension. JSM Atheroscler 1(3): 1015.